REMARKS

Following entry of the amendments, Claims 1-42 are pending in the application. Applicants have added new Claim 49. The amendments to the claims add no new matter and are fully supported by the specification as originally filed. In particular, support for new Claim 49 can be found on page 19, lines 7-8; page 32, lines 6-8, and elsewhere throughout the specification as originally filed.

Response to Restriction Requirement

In response to the restriction requirement, Applicants hereby elect to prosecute, with traverse, the claims of Group II, *i.e.*, claims1-12, 13, and 15-26.

The Examiner states that Claims 1-41 relate to three groups of inventions: Group I (Claims 1-12, in part, Claim 14), drawn to methods for modulating endothelial cell activity *in vitro*; Group II (Claims 1-12, in part, Claim 13 and Claims15-26), drawn to methods for modulating endothelial cell activity *in vivo*; and Group III (Claims 27-41), drawn to methods of treatment of inappropriate endothelial cell activity in a mammal. According to the Examiner, the claims in Groups I-III do not form a single general inventive concept under PCT Rule 12.1, since they relate to "regulation of endothelial cell activity by protein kinase C" which was disclosed prior to Applicants' effective filing date in Anrather et al. (1999) *J. Biol. Chem.* 274(19):13594-13603. Applicants respectfully disagree.

Anrather et al. does not teach "regulation of endothelial cell activity by protein kinase Cζ" ("PKCζ"). Anrather et al. only teaches that PKCζ is involved in the same pathway which regulates the activity of the transcription factor NFκB in endothelial cells. Anrather et al. does not provide any teachings regarding the role of PK Cζ in terms of any particular aspects of endothelial cell activity/functionality, such as endothelial cell permeability or the like. In fact, Anrather et al. does not link the modulation of NFκB activity to any particular endothelial cell functional outcome, either general or specific, and is completely silent regarding any functional outcome linked to NFκB activity.

Applicants' claims, on the other hand, recite a method of modulating endothelial cell activity. As stated on page 13, lines 17-20, of Applicants' specification, endothelial cell "activity" refers to "any one or more the *functional activities which an endothelial cell is capable of performing*, for example, as a result of stimulation by an extracellular agent such as thrombin,

VEGF or TNF." Intercellular and intracellular permeability are two non-limiting examples of such endothelial cell activities. Because Anrather et al. fails to disclose a method of modulating or regulating endothelial cell activity/functional activity which an endothelial cell is capable of performing the reference does not provide a proper basis for alleging that Applicants' claims lack unity of invention.

In short, the Anrather et al. reference does not teach or suggest modulation of endothelial cell activity. Anrather et al. is therefore not a proper basis for asserting that the claims lack a single inventive concept under PCT Rule 12.1. Accordingly Applicants respectfully request withdrawal of the restriction, and examination of Claims 1-41 and 49 on the merits.

Response to Species Election

Applicants elect, for the purposes of prosecution only and in compliance with linking claim practice to prosecute, with traverse, the following species: (A) intercellular permeability; (C)(i) A Thr^{410} Ala protein kinase C molecule; and (M) transcription. Election of each of the species is made with the understanding that such an election is for the purpose of examination only, in accordance with current linking claim practice. Pursuant to M.P.E.P. §809.02(a), Applicants maintain that upon a finding that the generic claim is allowable, Applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of the generic claim. Claims 1-5, 9, 23, 23, 15-19, 23, 26, and 49 read on the elected subject matter. For the reasons set forth below, however, Applicants maintain that the species election requirement is improper and request withdrawal of the same.

For the Claims in Group II, the Examiner requires Applicant to further elect a specific PKCζ modulator. Specifically, the Examiner has required Applicants to elect either a protein molecule or non-protein molecule. For the protein molecule, the Examiner further requires election between a Thr^{410} Ala protein kinase C, or angiopoietin. For the non-protein molecule, the Examiner further requires election of a nucleic acid molecule encoding protein kinase C, cherlerythrine chloride, or bisindoylmaleimide.

Applicants respectfully submit that the Examiner has improperly limited the scope of modulators to which Applicant is entitled to have examined. Specifically, the specification states that modulators of PKCζ functionality include small molecules that act as agonists or antagonists of the PCKζ expression product, antibodies, antisense nucleic acids which prevent transcription

or translation of PKCζ, antigens, RNA, DNAzymes, RNA apatmers, or other chemical entities. *See, e.g., Specification* at 19, lines 1-20. Accordingly, Applicants should be entitled to select, for the purposes of examination, any one of the modulators recited in the specification, such as antibodies or small molecule inhibitors of PKCζ, for example. Applicants should not be forced to select from an incomplete list of modulators. Solely in the interest of being fully responsive to the election requirement, Applicants have chosen the Thr^{410} Ala protein kinase C modulator. Given a complete list of modulators from which to choose, however, Applicants would have provisionally elected small molecule inhibitors of PKCζ. In view of the improperly limiting nature of the Examiner's species election requirement, Applicants request that it be withdrawn.

The Examiner has also required Applicants to elect (M) regulation of transcription or (N) regulation of translation. Applicants submit that this species election requirement is not only improperly limiting, but also does not entirely make sense, and respectfully request that the election requirement be withdrawn. In particular, the species identified by the Examiner would not encompass any modulators that act directly on the functionality or activity of the PKCζ expression product, such as Thr^{410}Ala PKCζ. Thr^{410}Ala PKC competitively inhibits endogenously produced and functionally active PKCζ and has no impact on either transcription or translation of the PKCζ gene. Likewise, small molecule inhibitors of PKCζ, which Applicants would have elected given a complete list of modulators in the previous species election, do not affect transcription or translation of PKCζ. Accordingly, the Examiner's requirement to elect modulation of transcription or modulation of translation is not relevant for all species of modulators, including for example the Thr^{410}Ala PKC modulator provisionally elected by Applicants, or, small molecule inhibitors modulators which Applicant would have elected. In view of the above, Applicants respectfully request withdrawal of the species election.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or

other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

The undersigned has made a good faith effort to respond to the Restriction Requirement. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to call the undersigned attorney to resolve such issues promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 12/27/07

By: Kathleen R. Mekjian
Registration No. 61,399
Attorney of Record
Customer No. 20,995
(619) 235-8550

4685104
122107